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Important Update — Additional Release of Newly Manufactured DOXIL® (doxorubicin HCl liposome injection)

Dear Healthcare Professional,

Due to the current critical shortage of DOXIL®, Janssen is continuing to request that the U.S. Food and Drug Administration (FDA) release additional lots of DOXIL® using an alternate manufacturing approach. Today, Janssen is pleased to announce that the FDA has released an additional lot of newly manufactured DOXIL® 20 mg/10 mL vials, Lot# 1208968.

The FDA is exercising its regulatory discretion to release this DOXIL®, Lot# 1208968, in an effort to address the current critical shortage of doxorubicin HCl liposome injection. This lot was produced through the alternate manufacturing approach which is described in our January 7, 2013 "Dear Healthcare Professional" letter. Our previous letters communicated the release of DOXIL® from Lot# 1207168, Lot# 1208966, and Lot# 1209507.

Although this manufacturing approach has not been approved by the FDA, the additional lot of newly manufactured DOXIL® has undergone a full Janssen internal review to ensure that it meets quality and safety standards. Janssen will continue to seek FDA approval for this manufacturing approach. Ensuring a sufficient supply of DOXIL® for physicians and their patients remains an urgent priority for Janssen Products.

To report adverse events, product quality complaints, or to request medical information related to DOXIL®, please contact Janssen Medical Information at 1-800-JANSSEN (1-800-526-7736).

Adverse events may also be reported to the FDA's MedWatch Adverse Event Reporting Program either online, by regular mail or by fax:

- Online: www.fda.gov/medwatch/report.htm
- Regular mail: use postage-paid FDA form 3500 available at www.fda.gov/MedWatch/getforms.htm. Mail to: MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787
- Fax: 1-800-FDA-0178

In the meantime, for ongoing updates, please visit www.DOXIL.com and www.DOXILSupply.com.

INDICATIONS

- DOXIL® is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy
- DOXIL® in combination with VELCADE® (bortezomib) is indicated for the treatment of patients with multiple myeloma who have not previously received VELCADE and have received at least one prior therapy

Please see Important Safety Information beginning on page 2.

IMPORTANT SAFETY INFORMATION

BOXED WARNINGS

Cardiotoxicity, infusion reaction, myelosuppression, liver impairment, substitution

- **The use of DOXIL® may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m^2**
  - **Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dose**
  - **Cardiac toxicity may also occur at lower cumulative doses (400 mg/m^2) in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy**
- **Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with DOXIL®. In most patients, these reactions have resolved within several hours to a day once the infusion is terminated. In some patients, reactions resolved with slowing of the infusion rate**
  - **Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have occurred. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use**
  - **The initial rate of infusion should be 1 mg/min to minimize the risk of infusion reactions**
- **Severe myelosuppression may occur**
- **DOXIL® dosage should be reduced in patients with impaired hepatic function**
- **Accidental substitution has resulted in severe side effects. Do not substitute for doxorubicin HCl on a mg per mg basis**

CONTRAINDICATIONS

- Patients with a history of hypersensitivity reactions to a conventional doxorubicin formulation or the components of DOXIL®

ADDITIONAL SAFETY INFORMATION

- Cardiac function should be carefully monitored
  - Congestive heart failure or cardiomyopathy may occur after discontinuation of anthracycline therapy
  - For patients with a history of cardiovascular disease, or if the results of cardiac monitoring indicate possible cardiac injury, the benefit of therapy must be weighed against the risk of myocardial injury
  - In the randomized multiple myeloma study, 25 patients (8%) in the VELCADE arm and 42 patients (13%) in the DOXIL® plus VELCADE arm experienced left ventricular ejection fraction decrease (defined as absolute decrease ≥15% over baseline or a ≥5% decrease below institutional lower limit of normal)
- Myelosuppression may occur; frequently monitor complete blood count (including platelet count), at least prior to each dose of DOXIL®
  - In patients with recurrent ovarian cancer, hematologic toxicity (based on platelet count or absolute neutrophil count) may require dose reduction or delay in administration of DOXIL®
  - In patients with multiple myeloma, hematologic toxicity (based on platelet count, absolute neutrophil count, hemoglobin level, or neutropenia with fever) may require dose reduction, delay in administration, or suspension of DOXIL® and/or VELCADE
  - Persistent severe myelosuppression may result in superinfection, neutropenic fever, or hemorrhage
  - Sepsis occurring during neutropenia has resulted in discontinuation of treatment and, in rare cases, death
- DOXIL® may potentiate the toxicity of other anticancer therapies, especially hematologic toxicities, when used in combination with other therapies that suppress bone marrow

Please see Important Safety Information continued on page 3.

IMPORTANT SAFETY INFORMATION (continued)

- Hand-foot syndrome (HFS) may occur during therapy with DOXIL®
  - Based on HFS toxicity grade, dose reduction, delay in administration, or discontinuation of DOXIL® may be required
  - HFS was generally observed after 2 to 3 cycles of treatment, but may occur earlier
    - The reaction was mild in most patients, resolving in 1 to 2 weeks
    - The reaction can be severe and debilitating in some patients, resulting in discontinuation of therapy
- DOXIL® is an irritant, not a vesicant; use precautions to avoid extravasation
- DOXIL® can cause fetal harm when used during pregnancy
- Because of the potential for serious adverse reactions in nursing infants, discontinue nursing during treatment with DOXIL®
- Recall reaction has occurred with DOXIL® administration after radiotherapy
- DOXIL® may interact with drugs known to interact with the conventional formulation of doxorubicin HCl
- In patients with recurrent ovarian cancer, the most common all-grade adverse reactions (ARs) ≥20% (DOXIL® vs topotecan, respectively) included: asthenia (40% vs 51%), fever (21% vs 31%), nausea (46% vs 63%), stomatitis (41% vs 15%), vomiting (33% vs 44%), diarrhea (21% vs 35%), anorexia (20% vs 22%), dyspnea (15% vs 23%), HFS (51% vs 1%), and rash (29% vs 12%)
  - In addition, 19% vs 52.3% reported alopecia (all grades)
  - Grade 3/4 hematologic ARs reported in ≥5% (DOXIL® vs topotecan, respectively) were neutropenia (12% vs 76%) and anemia (6% vs 29%)
- In patients with multiple myeloma, the most common all-grade ARs ≥20% (DOXIL® plus VELCADE vs VELCADE, respectively) included: neutropenia (36% vs 22%), thrombocytopenia (33% vs 28%), anemia (25% vs 21%), fatigue (36% vs 28%), pyrexia (31% vs 22%), asthenia (22% vs 18%), nausea (48% vs 40%), diarrhea (46% vs 39%), vomiting (32% vs 22%), constipation (31% vs 31%), mucositis/stomatitis (20% vs 5%), peripheral neuropathy (42% vs 45%), neuralgia (17% vs 20%), and rash (22% vs 18%)
  - In addition, 19% vs <1% reported HFS

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Sincerely,

Peter Callegari, MD
Vice President, Medical Affairs
Janssen Products, LP

Please see accompanying full Prescribing Information, including Boxed WARNINGS.

VELCADE is a registered trademark of Millennium Pharmaceuticals, Inc.

